Supporting information

In vivo activity of repurposed amodiaquine as a host-targeting therapy for the treatment of anthrax.

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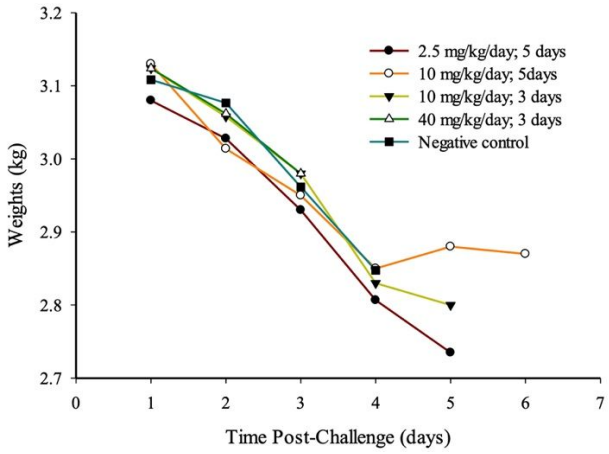

Figure S1: Weights of anthrax-infected rabbits receiving varying doses of AQ.

Weights of anthrax-infected NZW rabbits were measured in the absence or presence of varying doses of AQ administered for either 3 or 5 days. Animal weights were monitored once daily for as long as the animal lived. Treatment groups consisted of 5 rabbits each, while the control group consisted of 6 rabbits.

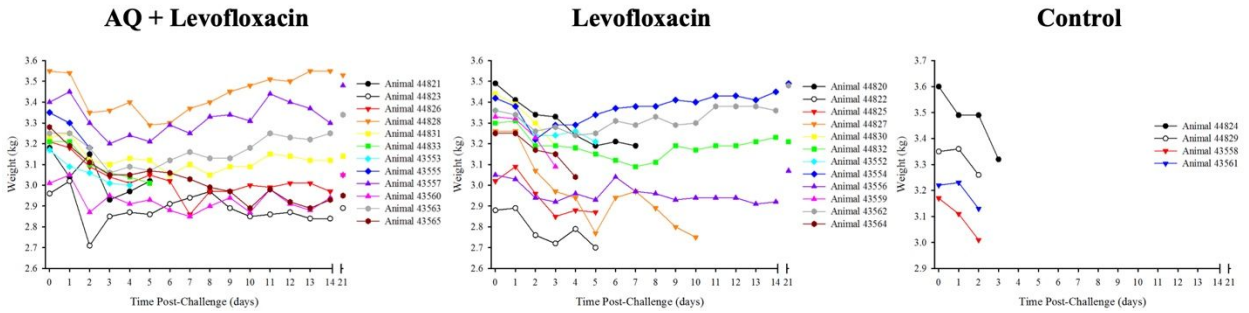

Figure S2: Weights of anthrax-infected rabbits receiving levofloxacin and AQ.

Weights of anthrax-infected NZW rabbits were measured for animals administered suboptimal dose (1.6 mg/kg/day) of levofloxacin (middle panel) or with 10 mg/kg/day of AQ in addition to levofloxacin (left panel). Animal weights for control rabbits were also measured (right panel). Animal weights were monitored once daily for as long as the animal lived. Treatment groups consisted of 12 rabbits each, while the control group consisted of 4 rabbits.

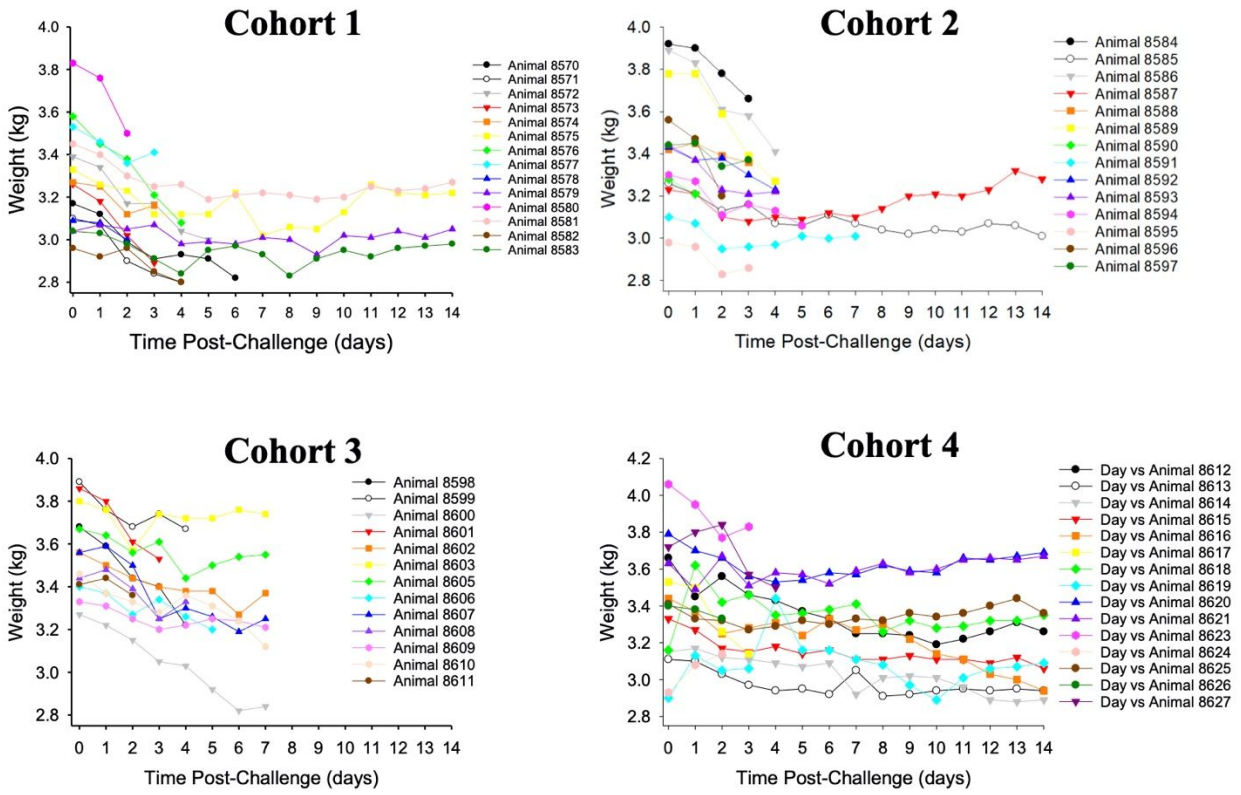

Figure S3: Weights of anthrax-infected rabbits receiving levofloxacin and delayed AQ treatment.

Weights of all anthrax-infected NZW rabbits were measured throughout the study. Due to the large study size, animals were divided into four cohorts. Each cohort included at least one animal from each group. Animal weights were monitored once daily for as long as the animal lived.

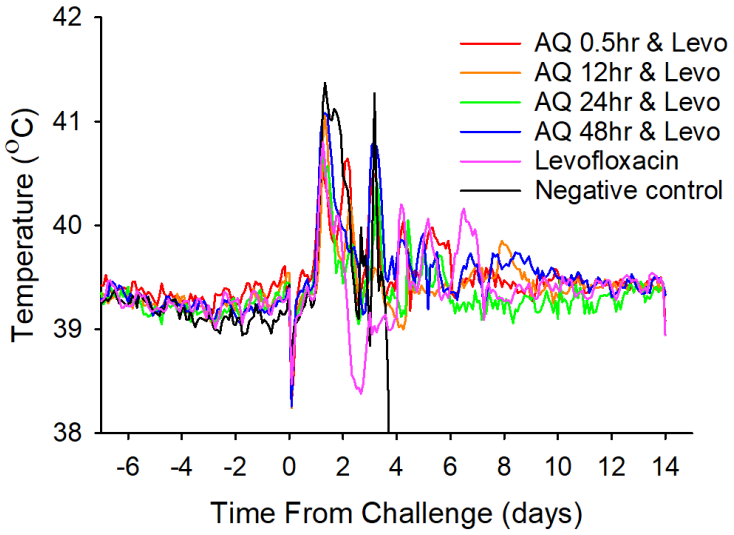

Figure S4: Temperature of anthrax-infected rabbits receiving levofloxacin and delayed AQ treatment.

The average core body temperatures of the treatment groups are presented as two-hour moving averages.

Table S1: Clinical observations of individual rabbits after intravenous administration of AQ and DEAQ.

					Number of days relative to start date		
					1	2	3
Drug	**Sex**	**Animal**	**Clinical Sign**	**Site**			
AQ - intravenous	Male	001	No abnormalities detected		X	X	X
			Main sacrifice		·	·	X
		002	No abnormalities detected		X	X	X
			Main sacrifice		·	·	X
		003	No abnormalities detected		X	X	X
			Main sacrifice		·	·	X
	Female	104†	No abnormalities detected		X	X	X
			Main sacrifice		·	·	X
		005	Ataxia		S	·	·
			Convulsion		E	·	·
			Nystagmus	Left	S	·	·
			Tachypnea		M	·	·
			Tremors		E	·	·
			Weakness		S	·	·
			Removed from Study		X	·	·
		006	Convulsion		E	·	·
			Hypoactivity ‡		S	·	·
			Tachypnea		M	·	·
			Removed from Study		X	·	·
DEAQ - intravenous	Male	007	No abnormalities detected		X	X	X
			Main sacrifice		·	·	X
		008	No abnormalities detected		X	X	X
			Main sacrifice		·	·	X
		009	No abnormalities detected		X	X	X
			Main sacrifice		·	·	X
	Female	010	No abnormalities detected		X	X	X
			Main sacrifice		·	·	X
		011	No abnormalities detected		X	X	X
			Hypoactivity		S	·	·
			Main sacrifice		·	·	X
		012	No abnormalities detected		X	X	X
			Main sacrifice		·	·	X

Severity Codes: X = Present; S = Slight; M = Moderate; E = Extreme

†Replacement animal. Female rabbit (004) died immediately post-dose.
‡Hypoactivity increased in severity (to extreme) after a few minutes when the other signs showed.

Clinical observations of individual male and female NZW rabbits were monitored after animals were given a single dose of 10 mg/kg of either AQ or DEAQ intravenously. Clinical signs were documented on the day of occurrence, the severity of clinical sign(s), and site of clinical sign(s),

if available. The animals were monitored for three days post-dose, if not removed from the study prior.

Table S2: Clinical observations of individual rabbits after oral administration of AQ.

					Number of days relative to start date		
					1	2	3
Drug	**Sex**	**Animal**	**Clinical Sign**	**Site**			
AQ - oral	Male	001	No abnormalities detected		X	X	X
			Main sacrifice		·	·	X
		002	No abnormalities detected		X	·	X
			Few feces		·	S	·
			Main sacrifice		·	·	X
		003	No abnormalities detected		X	X	X
			Main sacrifice		·	·	X
	Female	004	No abnormalities detected		X	X	X
			Main sacrifice		·	·	X
		005	No abnormalities detected		X	X	X
			Main sacrifice		·	·	X
		006	No abnormalities detected		X	·	·
			Few feces		·	M	M
			Reduced appetite		·	X	X
			Main sacrifice		·	·	X

Severity Codes: X = Present; S = Slight; M = Moderate

Clinical observations of individual male and female NZW rabbits were monitored after animals were given a single dose of 10 mg/kg of AQ orally. Clinical signs were documented on the day of occurrence, the severity of clinical sign(s), and site of clinical sign(s), if available. The animals were monitored for three days post-dose.

Table S3: Pharmacokinetics of individual rabbits after intravenous administration of AQ and DEAQ.

Drug	Sex	Animal	Analyte	T_{max} (hr)	C_{max} (µM)	$t_{1/2}$ (hr)	AUC_{last} (hr·µM)	AUC_{inf} (hr·µM)	Cl (ml/hr/kg)	V_z (ml/kg)
AQ	Male	001	AQ	0.083	11.10	8.9	8.50	8.61	3029	39059
		002		0.083	9.75	8.6	8.27	8.38	3144	38978
		003		0.083	13.54	9.4	7.30	7.39	3333	45370
			Mean	0.083	11.47	9.0	8.02	8.13	3169	41136
			SD	0.000	1.92	0.4	0.63	0.65	153	3667
	Female	104†	AQ	0.0833	19.64	9.3	15.37	15.58	1668	22366
		005‡		0.0833	10.23	n.a.	n.a.	n.a.	n.a.	n.a.
		006‡		0.0833	12.31	n.a.	n.a.	n.a.	n.a.	n.a.
			Mean	0.083	14.06	9.3	15.37	15.58	1668	22366
			SD	0.000	4.95	n.c.	n.c.	n.c.	n.c.	n.c.
	Male	001	DEAQ	4.0	0.39	22.9	9.03	12.17	n.c.	n.c.
		002		6.0	0.33	20.3	8.30	10.76	n.c.	n.c.
		003		6.0	0.28	17.9	7.12	8.58	n.c.	n.c.
			Mean	5.3	0.33	20.4	8.15	10.50	n.c.	n.c.
			SD	1.2	0.06	2.5	0.96	1.81	n.c.	n.c.
	Female	104	DEAQ	4.0	0.51	18.5	11.24	13.89	n.c.	n.c.
		005		n.a.	n.a.	n.a.	n.a.	n.a.	n.c.	n.c.
		006		n.a.	n.a.	n.a.	n.a.	n.a.	n.c.	n.c.
			Mean	4.0	0.51	18.5	11.24	13.89	n.c.	n.c.
			SD	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.
DEAQ	Male	007	DEAQ	0.083	7.29	12.1	20.69	21.73	1382	23280
		008		0.083	7.87	11.3	22.31	23.17	1296	21175
		009		0.083	7.41	14.8	24.59	26.86	1121	23939
			Mean	0.083	7.53	12.7	22.53	23.92	1266	22798
			SD	0.000	0.31	1.8	1.96	2.65	133	1444
	Female	010	DEAQ	0.083	8.27	12.4	20.84	21.95	1366	24456
		011		0.083	4.94	12.2	17.03	17.91	1681	29600
		012		0.083	7.38	13.3	18.94	20.24	1478	28406
			Mean	0.083	6.86	12.6	18.93	20.03	1508	27487
			SD	0.000	1.72	0.6	1.91	2.03	160	2692

†Replacement animal. Female rabbit (004) died immediately post-dose.
‡ Animals exhibited severe reactions post-dose and were euthanized after the 0.5 or 1 hr timepoint. Therefore, a complete drug concentration profile is not available.
n.a. not available.
n.c. not complete.

Pharmacokinetics of individual male and female NZW rabbits were determined after administered a single dose of 10 mg/kg of AQ or DEAQ intravenously. C_{max} denotes maximal plasma concentration, T_{max} time when C_{max} is achieved, $t_{1/2}$ plasma half-life, AUC_{last} area under the curve between first and last time points, AUC_{inf} area under the curve between first and last infinite time points, Cl clearance, and V_z volume of distribution. Mean values and standard deviations for each pharmacokinetic parameter were calculated for male or female rabbits, if possible.

Drug	Sex	Animal	Analyte	T_{max} (hr)	C_{max} (μM)	$t_{1/2}$ (hr)	AUC_{last} (hr·μM)	AUC_{inf} (hr·μM)
AQ	Male	001	AQ	1.00	0.85	1.9	2.46	2.66
		002		2.00	0.99	3.9	5.31	5.39
		003		1.00	0.56	3.4	2.79	3.60
			Mean	1.00	0.80	3.1	3.52	3.88
			SD	0.60	0.22	1.0	1.56	1.39
	Female	004	AQ	2.00	0.89	1.9	3.10	3.39
		005		2.00	1.08	4.5	5.11	5.22
		006		1.00	1.22	4.6	5.83	5.93
			Mean	2.00	1.07	3.7	4.68	4.84
			SD	0.60	0.16	1.5	1.42	1.31
	Male	001	DEAQ	1.00	1.86	12.4	20.03	21.56
		002		2.00	2.90	11.9	35.49	38.38
		003		2.00	1.39	9.6	22.68	23.57
			Mean	2.00	2.05	11.3	26.07	27.84
			SD	0.60	0.77	1.5	8.26	9.19
	Female	004	DEAQ	2.00	3.42	10.9	28.23	29.88
		005		2.00	2.56	11.3	32.27	34.29
		006		1.00	3.14	9.4	39.18	40.48
			Mean	2.00	3.04	10.5	33.23	34.88
			SD	0.60	0.44	1.0	5.54	5.33

Table S4: Pharmacokinetics of individual rabbits after oral administration of AQ. Pharmacokinetics of individual male and female NZW rabbits were determined after administered a single dose of 10 mg/kg of AQ orally. C_{max} denotes maximal plasma concentration, T_{max} time when C_{max} is achieved, $t_{1/2}$ plasma half-life, AUC_{last} area under the curve between first and last time points, AUC_{inf} area under the curve between first and last infinite time points, Cl clearance, and V_z volume of distribution. Mean values and standard deviations for each pharmacokinetic parameter were calculated for male or female rabbits.

		Challenge											
Post-Challenge (days)	***n* (M/F)**	**-7**	**0**	**0**	**0.5**	**1.0**	**1.5**	**2.0**	**2.5**	**3**	**3.5**	**4**	**4.5**
Post-Challenge (hours)		-168	0	0.08	12	24	36	48	60	72	84	96	108
AQ – 5 mg/kg* Group 1	5 (3/2)	x	-	AQ	AQ	AQ x	AQ	AQ x	AQ	x	-	-	-
AQ – 20 mg/kg* Group 2	5 (3/2)	x	-	AQ	AQ	AQ x	AQ	AQ x	AQ	x	-	-	-
Control – Untreated Group 3	6 (3/3)	x	-	-	-	x	-	x	-	x	-	-	-
AQ – 1.25 mg/kg* Group 4	5 (2/3)	x	-	AQ	AQ	AQ x	AQ	AQ x	AQ	AQ x	AQ	AQ	AQ
AQ – 5 mg/kg* Group 5	5 (2/3)	x	-	AQ	AQ	AQ x	AQ	AQ x	AQ	AQ x	AQ	AQ	AQ

*Animals are administered amodiaquine twice daily via orogastric tube.
x Blood collection (for antigenemia and bacteremia).
AQ Amodiaquine.

Table S5: Therapeutic dosing of AQ and blood collection schedule of anthrax-infected rabbits. Anthrax-infected NZW white rabbits were administered varying doses of AQ for either 3 or 5 days at the time of aerosol exposure to 200 LD_{50} of purified *B. anthracis* Ames spores. Blood samples of animals were collected prior to the anthrax challenge and once daily for three days post-challenge.

Antigenemia Table		PA (ng/mL)													
	Rabbit #	Pre-Bleed	24 h PC	48 h PC	72 h PC	7 d PC	10 d PC	14 d PC	Terminal	% Survival	Days Alive	X Days Alive	s.d	Hours Alive	X Hours Alive	s.d.
2.5 mg/kg/day 5 days	8830	0	1.13	7.58	>100				n/a	0%	3.69	2.67	1.12	89	64.00	26.99
	8831	0	0.29	4.25	>100				n/a		3.57			86		
	8833	0	23.67						n/a		1.43			34		
	8838	0	84.90	>100	>100						3.14			75		
	8841	0	76.73						n/a		1.50			36		
10 mg/kg/day 5 days	8832	0	55.91	>100	n/a					0%	3.09	3.67	1.22	74	88.00	29.42
	8834	0	1.17	23.65	>100				n/a		4.78			115		
	8835	0	15.45	>100					n/a		2.45			59		
	8839	0	0.00	0.00	9.16				n/a**		5.17			124		
	8842	0	9.48	>100					n/a		2.85			68		
10 mg/kg/day 3 days	6971	0	9.45	>100	n/a					0%	4.01	3.68	0.33	96	88.20	7.76
	6974	0	0.07	60.76	n/a						3.89			93		
	6977	0	3.30	*	n/a						3.41			82		
	6980	0	0.27	8.43	n/a						3.83			92		
	6982	0	0.07	>100	n/a						3.24			78		
40 mg/kg/day 3 days	6970	0	5.88	>100					>100	0%	2.33	1.90	0.50	56	45.60	11.99
	6973	0	14.20	>100							1.97			47		
	6976	0	33.19	n/a							2.02			49		
	6979	0	0.81	n/a					>100		2.14			51		
	6981	0	1.79								1.05			25		
Neg Control	6972	0	14.92	>100						0%	2.52	2.96	0.29	60	71.00	7.01
	6975	0	14.97	*	n/a				>100		2.89			69		
	6978	0	2.49	>100	n/a						3.39			81		
	8836	0	1.05	>100					n/a		2.87			69		
	8837	0	18.01	>100	>100						3.11			75		
	8840	0	43.75	>100	>100						2.98			72		

Table S6: Anthrax-related events of individual rabbits after oral administration of AQ. Survival, bacteremia, and antigenemia (PA concentration in serum) of individual male and female NZW rabbits were determined in the absence or presence of various single doses of AQ. PC stands for Post Challenge. Numbers denote the PA antigen concentrations in blood at the designated times, while numbers in red font show the animals with bacteremia. * Not enough sample to assay. ** Terminal blood for 8839 was collected and cultured from a serum separator tube (SST), and not a Wampole tube. n/a = Sample taken for bacteremia analysis, but not for antigenemia analysis.

		Challenge																
Post-Challenge (days)	***n*‡**	**-7**	**0**	**0**	**0.5**	**1.0**	**1.5**	**2.0**	**2.5**	**3**	**3.5**	**4**	**4.5**	**5**	**7**	**10**	**14**	**21**
Post-Challenge (hours)		-168	0	0.5	12	24	36	48	60	72	84	96	108	120	168	240	336	504
AQ – 5 mg/kg* + Levofloxacin – 1.6 mg/kg†	12	x	-	AQ	AQ	AQ + Levo x	AQ	AQ + Levo x	AQ	AQ + Levo x	AQ	AQ + Levo x	AQ	Levo x	x	x	x	x
Levofloxacin – 1.6 mg/kg†	12	x	-	-	-	Levo x	-	Levo x	-	Levo x	-	Levo x	-	Levo x	x	x	x	x
Control – Untreated	4	x	-	-	-	x	-	x	-	x	-	x	-	x	x	x	x	x

*Animals are administered amodiaquine twice daily via orogastric tube.
† Animals are administered levofloxacin once daily intravenously.
‡ Even number of males and females.
x Blood collection (for antigenemia and bacteremia).
AQ Amodiaquine.

Table S7: Therapeutic dosing and blood collection schedule of anthrax-infected rabbits receiving levofloxacin and AQ. Anthrax-infected NZW white rabbits were administered with a suboptimal dose (1.6 mg/kg/day) of levofloxacin or with 10 mg/kg/day of AQ in addition to levofloxacin. Blood samples of animals were collected prior to the anthrax challenge, once daily for five days post-challenge, and several times after seven days post-challenge if animals still had not succumbed to infection.

Serum PA concentration	(ng/ml)													
	Rabbit #	Pre-Bleed	24 h PC	48 h PC	72 h PC	96 h PC	120 h PC	7 days PC	10 days PC	14 days PC	21 days PC	Terminal	% Survival	Days Alive	Hours Alive
Levo Only	44820	0.00	33.16	34.71	14.13	151.14	674.92	59720.40					33%	6.98	167
	44822	0.00	16.46	203.04	273.02	962.15	5932.78							5.00	120
	44825	0.00	3.44	18.04	43.71	42.78	72.86							4.89	117
	44827	0.00	236.64	93.21	150.27	1088.40	492.40	4.36	0.05					10.02	240
	44830	0.00	4.52	132.67	1318.59							+		4.02	96
	44832	0.00	6.67	19.74	22.44	7.94	4.21	0.00	0.00	0.02	0.00	n/a		21.00	504
	43552	0.00	2.96	22.27	105.64	481.10	3629.02					+		5.89	141
	43554	0.00	7.29	14.59	17.44	3.78	2.37	0.00	0.00	0.00	0.00	n/a		21.00	504
	43556	0.00	0.95	7.48	3.00	4.08	1.17	76.94	0.00	0.04	0.00	n/a		21.00	504
	43559	0.00	55.29	148.09	3100.38	8189.92								4.00	96
	43562	0.00	0.24	2.11	18.86	3.43	0.97	0.00	0.00	0.02	0.00	n/a		21.00	504
	43564	0.00	3.48	28.49	983.95	69404.46								3.88	93
AQ & Levo	44821	0.00	0.79	49.20	251.25	941.06	238653.02						67%	5.02	121
	44823	0.00	5.21	7.54	ND	100.24	295.18	0.00	0.00	0.00	0.00	n/a		21.00	504
	44826	0.00	1.19	15.64	5.06	9.84	19.12	0.00	0.00	0.02	0.00	n/a		21.00	504
	44828	0.00	40.47	17.75	4.93	3.03	0.91	0.00	0.00	0.00	0.00	n/a		21.00	504
	44831	0.00	2.55	10.68	63.05	57.22	47.98	0.00	0.00	0.04	0.00	n/a		21.00	504
	44833	0.00	0.11	6.42	28.06	99.46	168.95					-		5.32	128
	43553	0.00	4.44	51.74	361.46	444.39						-		4.79	115
	43555	0.00	17.71	410.46								+		2.70	65
	43557	0.00	0.81	5.14	3.20	1.70	0.63	0.00	0.00	0.00	0.00	n/a		21.00	504
	43560	0.00	1.14	5.01	1.27	1.54	0.00	0.00	0.00	0.00	0.00	n/a		21.00	504
	43563	0.00	0.00	3.70	21.22	58.02	5.81	0.17	0.00	0.00	0.00	n/a		21.00	504
	43565	0.00	3.11	42.42	58.83	9.86	27.24	34.69	0.00	0.00	0.00	n/a		21.00	504
Neg. Control	44824	0.00	2.85	14.48	1492.90								0%	2.91	70
	44829	0.00	5.94	1887.30										2.79	67
	43558	0.00	0.34	1555.41								+		2.29	55
	43561	0.00	42.56	828.31								+		2.51	60

Table S8: Anthrax-related events of individual rabbits after oral administration of AQ. Survival, bacteremia, and antigenemia (PA concentration in serum) of individual male and female NZW rabbits were determined in the absence or presence of Levofloxacin with and without 10 mg/kg/day of AQ. Numbers denote the PA antigen concentrations in blood at the designated times, while numbers in red font show the animals with bacteremia. PC stands for Post Challenge. ND - not determined for serum PA concentration.

			Challenge																	
Post-Challenge (days)	***n*‡**	**-7**	**0**	**0**	**0.5**	**1.0**	**1.5**	**2.0**	**2.5**	**3**	**3.5**	**4**	**4.5**	**5**	**5.5**	**6**	**6.5**	**7**	**10**	**14**
Post-Challenge (hours)		-168	0	0.5	12	24	36	48	60	72	84	96	108	120	132	144	156	168	240	336
AQ (0.5h) – 5 mg/kg* + Levofloxacin – 1.6 mg/kg†	12	x§	-	AQ	AQ x	AQ + Levo x	AQ	AQ + Levo x	AQ	AQ + Levo x§	AQ	AQ + Levo x	AQ	Levo x	-	-	-	x§	x§	x§
AQ (12h) – 5 mg/kg* + Levofloxacin – 1.6 mg/kg†	12	x§	-	-	AQ x	AQ + Levo x	AQ	AQ + Levo x	AQ	AQ + Levo x§	AQ	AQ + Levo x	AQ	AQ + Levo x	-	-	-	x§	x§	x§
AQ (24h) – 5 mg/kg* + Levofloxacin – 1.6 mg/kg†	12	x§	-	-	x	AQ + Levo x	AQ	AQ + Levo x	AQ	AQ + Levo x§	AQ	AQ + Levo x	AQ	AQ + Levo x	AQ	-	-	x§	x§	x§
AQ (48h) – 5 mg/kg* + Levofloxacin – 1.6 mg/kg†	12	x§	-	-	x	Levo x	-	AQ + Levo x	AQ	AQ + Levo x§	AQ	AQ + Levo x	AQ	AQ + Levo x	AQ	AQ	AQ	x§	x§	x§
Levofloxacin – 1.6 mg/kg†	4	x§	-	-	x	Levo x	-	Levo x	-	Levo x§	-	Levo x	-	Levo x	-	-	-	x§	x§	x§
Control – Untreated	4	x§	-	-	x	x	-	x	-	x§	-	x	-	x	-	-	-	x§	x§	x§

*Animals are administered amodiaquine twice daily via orogastric tube.
† Animals are administered levofloxacin once daily intravenously.
‡ Even number of males and females.
x Blood collection (for antigenemia and bacteremia).
§ Anti-PA IgG assessment.
AQ Amodiaquine.

Table S9: Therapeutic dosing and blood collection schedule of anthrax-infected rabbits receiving levofloxacin and delayed AQ treatment. Anthrax-infected NZW white rabbits were administered with a suboptimal dose (1.6 mg/kg/day) of levofloxacin or with 10 mg/kg/day of AQ in addition to levofloxacin at 30 minutes, 12 hours, 24 hours, or 48 hours post-infection. All treatments were given for a total of five days from start time. Blood samples of animals were collected prior to the anthrax challenge, at least once daily for five days post-challenge, and several times after seven days post-challenge if animals still had not succumbed to infection. Assessment for anti-PA IgG was conducted for all animals prior to challenge, as well as 3-, 7-, 10-, and 14-days post anthrax challenge.

Side Effect	# Articles	Side Effect	# Articles
Agranulocytosis	13	Oedema	3
Jaundice	7	Pruritus	3
Nausea	7	Abdominal discomfort	2
Vomiting	7	Ascites	2
Hepatitis	6	Asterixis	2
Headache	5	Atrophy	2
Malaise	5	Blindness	2
Encephalopathy	4	Chills	2
Hepatic encephalopathy	4	Cholestasis	2
Necrosis	4	Corneal deposits	2
Rash	4	Diarrhea	2
Abdominal pain	3	Erythema	2
Anorexia	3	Gastroenteritis	2
Asthenia	3	Hepatotoxicity	2
Fatigue	3	Herpes simplex	2
Fibrosis	3	Mucosal pigmentation	2
Hepatitis a	3	Renal failure	2
Hepatitis b	3	Sepsis	2
Inflammation	3	Skin reaction	2
Lethargy	3	Thrombocytopenia	2
Melanosis	3	Ulcer	2
Neutropenia	3		

Table S10: Identification of side effects in AQ safety articles via Python. A list of general 7,058 side-effects, which excluded the side-effect “malaria”, was utilized. The number of articles that mention a side effect from the list is counted in the set of 25 AQ safety articles extracted from the manual systemic literature review. Python Parser Library was used to search words and phrases in the main body of each article (excluding references). Only side effects mentioned in more than one article were included in this Table.

Side Effect	# Articles	Side Effect	# Articles
Agranulocytosis	13	Asthenia	3
Jaundice	9	Atrophy	3
Nausea	8	Cytopenia	3
Headache	7	Fatigue	3
Vomiting	7	Fibrosis	3
Hepatitis	6	Hepatitis a	3
Malaise	5	Hepatitis b	3
Encephalopathy	4	Inflammation	3
Melanosis	4	Lethargy	3
Necrosis	4	Oedema	3
Neutropenia	4	Rash	3
Pruritus	4	Skin reaction	3
Abdominal pain	3	Visual disturbance	3
Anorexia	3		

Table S11: Identification of side effects in AQ safety articles via Matlab. A list of general 7,058 side-effects, which excluded the side-effect "malaria", was utilized. The number of articles that mention a side effect from the list is counted in the set of 25 AQ safety articles extracted from the manual systemic literature review. Matlab Text Analytics Toolbox was used to search words and phrases in the main body of each article (excluding references). Only side effects mentioned in more than two articles were included in this Table.

Side Effect	# Articles	Side Effect	# Articles
Vomiting	462	Lethargy	52
Agranulocytosis	233	Malaise	51
Headache	223	Plasmodium falciparum infection	51
Nausea	199	Inflammation	50
Hepatitis	176	Renal failure	43
Diarrhea	174	Meningitis	38
Abdominal pain	166	Liver injury	37
Anorexia	131	Erythema	36
Pruritus	131	Oedema	36
Hepatotoxicity	127	Abdominal discomfort	30
Hypersensitivity	123	Dermatitis	30
Rash	109	Leprosy	29
Tuberculosis	104	Influenza	27
Neutropenia	97	Hepatitis b	26
Jaundice	89	Thrombocytopenia	25
Fatigue	79	Genetic polymorphism	24
Necrosis	68	Aspiration	23
Coma	64	Phagocytosis	22
Arthritis	61	Fasting	21
Chills	59	Gastroenteritis	21
Splenomegaly	59	Rigors	21
Asthenia	52		

Table S12: Identification of side effects in AQ articles via Python. A list of 148 side-effects previously found in the set of 25 AQ safety articles extracted from the manual systemic literature review was utilized. The number of articles that mention a side effect from this selected list is counted in a large publication database of all available AQ papers (1,807 articles in pdf format). Python Parser Library was used to search words and phrases in the main body of each article (excluding references). Only side effects mentioned in more than 20 articles were included in this Table.

Side Effect	# Articles	Side Effect	# Articles
Vomiting	130	Jaundice	33
Anemia	68	Pneumonia	29
Nausea	60	Plasmodium falciparum infection	24
Headache	59	Anorexia	23
Agranulocytosis	55	Splenomegaly	22
Diarrhea	47	Dizziness	20
Hepatitis	44	Malaise	20
Convulsion	38	Neutropenia	20
Pruritus	38	Rash	19
Malnutrition	36	Hypersensitivity	18
Abdominal pain	33		

Table S13: Identification of side effects in AQ articles via Matlab. A list of general 7,058 side-effects, which excluded the side-effect "malaria", was utilized. The number of articles that mention a side effect from the list is counted in the set of 411 AQ articles extracted from the manual systemic literature review. Matlab Text Analytics Toolbox was used to search words and phrases in the main body of each article (excluding references).